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(FILE 'HOME' ENTERED AT 14:07:57 ON 26 JUL 2000)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, PHAR' ENTERED AT 14:09:17 ON

26

JUL 2000

L1 213724 S COBALAMIN OR FOLATE OR S-ADENOSYL(W)METHIONINE OR BETAIN  
OR  
L2 1223280 S CANCER OR CARDIOVASCULAR(W)DISEASE OR DOWN?(W)SYNDROME  
L3 5662 S L1 AND L2  
L4 108 S METHIONINE(W)SYNTHASE(W)REDUCTASE OR MTRR  
L5 5 S L3 AND L4  
L6 20517 S NEURAL(W)TUBE  
L7 11 S L1 AND L6 AND L4  
L8 3 DUP REM L5 (2 DUPLICATES REMOVED)  
L9 5 DUP REM L7 (6 DUPLICATES REMOVED)

=> d 1-3 bib ab 18

L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS

AN 2000:493687 CAPLUS

TI Human **methionine synthase reductase**:  
cloning, and methods for evaluating risk of neural tube defects,  
**cardiovascular disease, cancer, and down's**  
syndrome

IN Gravel, Roy A.; Rozen, Rima; Leclerc, Daniel; Wilson, Aaron; Rosenblatt,  
David

PA McGill University, Can.

SO PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	WO 2000042196	A2	20000720	WO 2000-IB209	20000114
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRAI US 1999-232028 19990115

US 1999-371347 19990810

AB The invention features a novel gene encoding **methionine synthase reductase**. The invention also features a method for detecting an increased likelihood of hyperhomocysteinemia and, in turn, an increased or decreased likelihood of neural tube defects, **cardiovascular disease, Down's Syndrome or cancer**. The invention also features therapeutic methods for treating and/or reducing the risk of **cardiovascular disease, Down's Syndrome, cancer, or neural tube defects**. Also provided are the sequences of the human **methionine synthase reductase** gene and protein and compounds and kits for performing the methods of the invention.

L8 ANSWER 2 OF 3 MEDLINE

AN 2000250198 MEDLINE

DUPLICATE 1

DN 20250198  
 TI 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review.  
 AU Botto L D; Yang Q  
 CS Birth Defects and Pediatric Genetics Branch, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA... lcb9@cdc.gov  
 SO AMERICAN JOURNAL OF EPIDEMIOLOGY, (2000 May 1) 151 (9) 862-77. Ref: 109  
 Journal code: 3H3. ISSN: 0002-9262.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, ACADEMIC)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 200007  
 EW 20000702  
 AB The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism. The MTHFR gene is located on chromosome 1 (1p36.3), and two common alleles, the C677T (thermolabile) allele and the A1298C allele, have been described. The population frequency of C677T homozygosity ranges from 1% or less among Blacks from Africa and the United States to 20% or more among Italians and US Hispanics. C677T homozygosity in infants is associated with a moderately increased risk for spina bifida (pooled odds ratio = 1.8; 95% confidence interval: 1.4, 2.2). Maternal C677T homozygosity also appears to be a moderate risk factor (pooled odds ratio = 2.0; 95% confidence interval: 1.5, 2.8). The A 1298C allele combined with the C677T allele also could be associated with an increased risk for spina bifida. Some data suggest that the risk for spina bifida associated with C677T homozygosity may depend on nutritional status (e.g., blood folate levels, intake of vitamins) or on the genotype of other folate-related genes (e.g., cystathionine-beta-synthase and methionine synthase reductase). Studies of the C677T allele in relation to oral clefts, Down syndrome, and fetal anticonvulsant syndrome either have yielded conflicting results or have not been yet replicated.

L8 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2  
 AN 2000:277064 BIOSIS  
 DN PREV200000277064  
 TI Polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) and in the methionine synthase reductase (MTRR) genes increase maternal risk of Down syndrome.  
 AU Yi, P.; Hobbs, C.; Melnyk, S.; Sherman, S.; Gravel, R.; Wu, Q.; Rozen, R.; James, S. J.  
 SO FASEB Journal, (March 15, 2000) Vol. 14, No. 4, pp. A231. print.. Meeting Info.: Annual Meeting of Professional Research Scientists: Experimental Biology 2000. San Diego, California, USA April 15-18, 2000 Federation of American Societies for Experimental Biology . ISSN: 0892-6638.  
 DT Conference  
 LA English  
 SL English

=> d 1-5 bib ab 19

L9 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS

AN 2000:493687 CAPLUS

TI Human **methionine synthase reductase**:  
cloning, and methods for evaluating risk of **neural tube**  
defects, cardiovascular disease, cancer, and down's syndrome

IN Gravel, Roy A.; Rozen, Rima; Leclerc, Daniel; Wilson, Aaron; Rosenblatt,  
David

PA McGill University, Can.

SO PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000042196	A2	20000720	WO 2000-IB209	20000114

W: CA, JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE

PRAI US 1999-232028 19990115

US 1999-371347 19990810

AB The invention features a novel gene encoding **methionine synthase reductase**. The invention also features a method for detecting an increased likelihood of hyperhomocysteinemia and, in turn, an increased or decreased likelihood of **neural tube** defects, cardiovascular disease, Down's Syndrome or cancer. The invention also features therapeutic methods for treating and/or reducing the risk of cardiovascular disease, Down's Syndrome, cancer, or **neural tube** defects. Also provided are the sequences of the human **methionine synthase reductase** gene and protein and compounds and kits for performing the methods of the invention.

L9 ANSWER 2 OF 5 SCISEARCH COPYRIGHT 2000 ISI (R)

AN 2000:337446 SCISEARCH

GA The Genuine Article (R) Number: 308ER

TI 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: A HuGE review

AU Botto L D (Reprint); Yang Q H

CS CTR DIS CONTROL & PREVENT, BIRTH DEFECTS & PEDIAT GENET BRANCH, NATL CTR  
ENVIRONM HLTH, MS F-45, ATLANTA, GA 30341 (Reprint)

CYA USA

SO AMERICAN JOURNAL OF EPIDEMIOLOGY, (1 MAY 2000) Vol. 151, No. 9, pp.  
862-877.

Publisher: OXFORD UNIV PRESS INC, JOURNALS DEPT, 2001 EVANS RD, CARY, NC  
27513.

ISSN: 0002-9262.

DT General Review; Journal

FS LIFE; CLIN

LA English

REC Reference Count: 109

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is  
involved

in **folate** metabolism. The MTHFR gene is located on chromosome 1  
(1p36.3), and two common alleles, the C677T (thermolabile) allele and the  
A1298C allele, have been described. The population frequency of C677T  
homozygosity ranges from 1% or less among Blacks from Africa and the  
United States to 20% or more among Italians and US Hispanics. C677T  
homozygosity in infants is associated with a moderately increased risk

for  
spina bifida (pooled odds ratio = 1.8; 95% confidence interval: 1.4,  
2.2).

~~Maternal C677T homozygosity also appears to be a moderate risk factor~~  
(pooled odds ratio = 2.0; 95% confidence interval: 1.5, 2.8). The A1298C allele combined with the C677T allele also could be associated with an increased risk for spina bifida. Some data suggest that the risk for

spina

bifida associated with C677T homozygosity may depend on nutritional status

(e.g., blood **folate** levels, intake of vitamins) or on the genotype of other **folate**-related genes (e.g., cystathionine-beta-synthase and **methionine synthase reductase**). Studies of the C677T allele in relation to oral clefts, Down syndrome, and fetal anticonvulsant syndrome either have yielded conflicting results or have not been yet replicated.

✓  
L9 ANSWER 3 OF 5 MEDLINE DUPLICATE 1  
AN 1999375459 MEDLINE  
DN 99375459  
TI A common variant in **methionine synthase reductase** combined with low **cobalamin** (vitamin B12) increases risk for spina bifida.  
AU Wilson A; Platt R; Wu Q; Leclerc D; Christensen B; Yang H; Gravel R A; Rozen R  
CS The Montreal Children's Hospital Research Institute, McGill University, Montreal, Quebec, Canada.  
NC HL58955-01 (NHLBI)  
SO MOLECULAR GENETICS AND METABOLISM, (1999 Aug) 67 (4) 317-23.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199911  
EW 19991105  
AB Impairment of **folate** and **cobalamin** (vitamin B(12)) metabolism has been observed in families with **neural tube** defects (NTDs). Genetic variants of enzymes in the homocysteine remethylation pathway might act as predisposing factors contributing to NTD risk. The first polymorphism linked to increased NTD risk was the 677C-->T mutation in methylenetetrahydrofolate reductase (MTHFR). We now report a polymorphism in **methionine synthase reductase (MTRR)**, the enzyme that activates **cobalamin**-dependent **methionine** synthase. This polymorphism, 66A-->G (I22M), has an allele frequency of 0.51 and increases NTD risk when **cobalamin** status is low or when the MTHFR mutant genotype is present. Genotypes and **cobalamin** status were assessed in 56 patients with spina bifida, 58 mothers of patients,  
97 control children, and 89 mothers of controls. Cases and case mothers were almost twice as likely to possess the homozygous mutant genotype when compared to controls, but this difference was not statistically significant. However, when combined with low levels of **cobalamin**, the risk for mothers increased nearly five times (odds ratio (OR) =  
4.8, 95% CI 1.5-15.8); the OR for children with this combination was 2.5 (95% CI 0.63-9.7). In the presence of combined MTHFR and **MTRR** homozygous mutant genotypes, children and mothers had a fourfold and threefold increase in risk, respectively (OR = 4.1, 95% CI 1.0-16.4; and OR = 2.9, 95% CI 0.58-14.8). This study provides the first genetic link between vitamin B(12) deficiency and NTDs and supports the multifactorial origins of these common birth defects. Investigation of this polymorphism in other disorders associated with altered homocysteine metabolism, such as vascular disease, is clearly warranted. Copyright 1999 Academic Press.

L9 ANSWER 4 OF 5 SCISEARCH COPYRIGHT 2000 ISI (R)  
AN 2000:182666 SCISEARCH

GA The Genuine Article (R) Number: 28844  
TI Molecular genetics of homocysteine metabolism  
AU Fodinger M (Reprint); Buchmayer H; SunderPlassmann G  
CS UNIV VIENNA, DEPT LAB MED, DIV MOL BIOL, WAHRINGER GURTEL 18-20, A-1090  
VIENNA, AUSTRIA (Reprint); UNIV VIENNA, DEPT INTERNAL MED 3, DIV NEPHROL

&  
DIALYSIS, A-1090 VIENNA, AUSTRIA

CYA AUSTRIA

SO MINERAL AND ELECTROLYTE METABOLISM, (JUL-DEC 1999) Vol. 25, No. 4-6, pp.  
269-278.

Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.

ISSN: 0378-0392.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 92

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Recent genetic studies have led to the characterization of molecular  
determinants contributing to the pathogenesis of hyperhomocysteinemia. In  
this article we summarize the current insights into the molecular  
genetics

of severe, moderate and mild hyperhomocysteinemia. We will consider  
deficiencies of the trans-sulfuration enzyme cystathionine beta-synthase  
(gene symbol: CBS), and the disturbances of the remethylation enzymes  
5,10-methylenetetrahydrofolate reductase (gene symbol: MTHFR),  
**methionine synthase** (gene symbol: MTR), and the recently  
identified **methionine synthase reductase**  
(gene symbol: **MTRR**). Furthermore, we will focus on clinically  
important genetic polymorphisms which are highly prevalent and thus of  
potential general interest. Copyright (C) 2000 S. Karger AG, Basel.

L9 ANSWER 5 OF 5 MEDLINE

DUPLICATE 2

AN 1999120880 MEDLINE

DN 99120880

TI [Molecular genetics of the remethylation of homocysteine].  
Genetique moleculaire de la remethylation de l'homocysteine.

AU Chango A; Parrot-Roulaud F; Nicolas J

CS Laboratoire de biochimie medicale et pediatrique, Inserm U. 308, 9, av.  
Foret-de-Haye, 54505 Vandoeuvre-l'es-Nancy, France.

SO ANNALES DE BIOLOGIE CLINIQUE, (1999 Jan-Feb) 57 (1) 37-42. Ref: 44  
Journal code: 4ZS. ISSN: 0003-3898.

CY France

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA French

FS Priority Journals

EM 199905

EW 19990503

AB In plasma of mothers with a child affected with a **neural**  
**tube** defect plasma homocysteine is often elevated, and attributed  
to a reduced **folate**-dependent homocysteine remethylation. There  
is strong evidence that folic acid prevents fasting moderate  
hyperhomocysteinemia. The pathophysiology of **neural tube**  
defect and interactions between genetic and nutritional factors that  
determine plasma homocysteine levels remain poorly understood.  
Investigations on genetic causes of moderate hyperhomocysteinemia are in  
progress. This mini-review focuses on molecular genetic knowledge of  
**folate**-dependent homocysteine remethylation in **neural**  
**tube** defect.

=> d his

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JUL 2000

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OR  
L2 1223280 S CANCER OR CARDIOVASCULAR(W)DISEASE OR DOWN?(W)SYNDROME  
L3 5662 S L1 AND L2  
L4 108 S METHIONINE(W)SYNTHASE(W)REDUCTASE OR MTRR  
L5 5 S L3 AND L4  
L6 20517 S NEURAL(W)TUBE  
L7 11 S L1 AND L6 AND L4  
L8 3 DUP REM L5 (2 DUPLICATES REMOVED)  
L9 5 DUP REM L7 (6 DUPLICATES REMOVED)  
L10 302599 S POLYMORPHI?  
L11 1242982 S L2 OR L6  
L12 8 S L11 AND L4 AND L10  
L13 4 DUP REM L12 (4 DUPLICATES REMOVED)

=> d au ti so 1-4 l13

L13 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1  
AU Yi, P.; Hobbs, C.; Melnyk, S.; Sherman, S.; Gravel, R.; Wu, Q.; Rozen,  
R.;  
James, S. J.  
TI **Polymorphisms** in the methylenetetrahydrofolate reductase (MTHFR)  
and in the **methionine synthase reductase** (  
**MTRR**) genes increase maternal risk of Down  
**syndrome**.  
SO FASEB Journal, (March 15, 2000) Vol. 14, No. 4, pp. A231. print..  
Meeting Info.: Annual Meeting of Professional Research Scientists:  
Experimental Biology 2000. San Diego, California, USA April 15-18, 2000  
Federation of American Societies for Experimental Biology  
. ISSN: 0892-6638.

L13 ANSWER 2 OF 4 MEDLINE DUPLICATE 2  
AU Wilson A; Platt R; Wu Q; Leclerc D; Christensen B; Yang H; Gravel R A;  
Rozen R  
TI A common variant in **methionine synthase**  
**reductase** combined with low cobalamin (vitamin B12) increases risk  
for spina bifida.  
SO MOLECULAR GENETICS AND METABOLISM, (1999 Aug) 67 (4) 317-23.  
Journal code: CXY. ISSN: 1096-7192.

L13 ANSWER 3 OF 4 SCISEARCH COPYRIGHT 2000 ISI (R)  
AU Fodinger M (Reprint); Buchmayer H; SunderPlassmann G  
TI Molecular genetics of homocysteine metabolism  
SO MINERAL AND ELECTROLYTE METABOLISM, (JUL-DEC 1999) Vol. 25, No. 4-6, pp.  
269-278.  
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.  
ISSN: 0378-0392.

L13 ANSWER 4 OF 4 MEDLINE  
AU Chango A; Parrot-Roulaud F; Nicolas J

T1 ~~[Molecular genetics of the remethylation of homocysteine]~~  
Genetique moleculaire de la remethylation de l'homocysteine.  
SO ANNALES DE BIOLOGIE CLINIQUE, (1999 Jan-Feb) 57 (1) 37-42. Ref: 44  
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